TREATMENT OF ACNE VULGARIS AND SENILE KERATOSES WITH VITAMIN A: RESULTS OF A CLINICAL EXPERIMENT

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Recent advances in our knowledge of the relationship between vitamin A and cutaneous disorders are numerous but not spectacular. While a number of new dermatoses have been added to the list of those which appear to respond at least occasionally to the administration of vitamin A, such as leukoplakia vulvae (1), porokeratosis Mibelli (2), keratosis blennorrhagica (3), acrokeratosis verruciformis (4), pili torti (5), and hyperkatosis follicularis et parafollicularis in cutem penetrans (6), studies of the working mechanism of the substance have not been particularly successful. It was determined by chemical assay (7) that there is little evidence to show that dermatologic conditions influence or are influenced by the amount of vitamin A in the blood plasma. On the other hand, determination of the level of the vitamin in the blood serum of 8 normal persons and 11 patients with dermatologic disease following the administration of massive doses showed abnormally flat curves in patients with keratosis follicularis, congenital dyskeratosis and infantile eczema (8). The response to the dark-adaptation test of patients with various dermatoses was reported not to differ significantly from that of persons with normal skins (9). It is likely that the advent of the aqueous preparations of the vitamin will facilitate bio-chemical studies; early reports (10) indicate their greater ability to raise the vitamin A level of the blood serum.

We have been concerned for several years with the effect of the vitamin on the pathologic changes of the pilo-sebaceous follicle in acne vulgaris (11), a subject on which other investigators have recently reported their observations (12, 13). Since we were unable to arrive at definite conclusions about the efficacy of the therapy we decided to conduct a controlled clinical experiment which might yield more accurate data. After the experiment was well under way we read with interest the report of an exceptionally well-controlled and conducted experiment on the effect of vitamin A therapy on keratoses (14). The importance of a practical method for the control of precancerous lesions of the keratosis type was the reason for the second study.

MATERIALS AND METHODS

A. Experimental Therapy of Acne Vulgaris. Sixty-five students attending the University of California at Los Angeles were the subjects of the experiment. Some participated as the result of an advertisement run in the college newspaper, which asked the cooperation of suitable students, and others were referred by physicians of the student Health Service.[1] The only subjects rejected for the

[1] We are indebted to Drs. Stanley C. Anderson, Stanley Chambers and Donald S. MacKinnon and to the nurses and secretaries of the Student Health Service for making the study possible.

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TABLE 1

*Data about forty-three patients with acne vulgaris who completed experiment**

PATIENT†	RACE	SEX	AGE	MARITAL STATUS	TYPE OF ACNE	SEVERITY OF LESIONS	LENGTH OF TREATMENT	NUMBER OF TIMES OBS.	COMMENT	X—WORSE WHEN Rx STOPPED
			Yrs.				*mos.*			
1. K. L.	w	M	26	s	com	Moderate	1	1		1
(2.) M. B.	w	I	20	s	pap	Moderate	6	4	Control	2
3. J. F.	w	M	25	m	pap-pus	Slight	6	4		3
4. E. W.	w	M	22	s	cys	Slight	7	4		4
5. J. H.	w	M	18	s	pap-pus	Slight	7	4		5
(6.) R. C.	w	F	18	s	pap	Slight	6	4	Control	6
7. J. Z.	w	F	18	s	com-pap-pus	Moderate	2	3		7
(8.) V. B.	w	F	19	s	pap	Moderate	7	5	Control	8
9. R. G.	w	M	24	s	pap-pus	Moderate	2	2		9
10. T. D.	w	M	26	s	pap-pus	Moderate	5	4		x10
11. A. M.	w	F	18	s	com-pap-pus	Moderate	2	2		11
12. L. M.	w	M	18	s	com-pap-pus	Slight	2	2		12
13. V. N.	w	F	25	m	com-pap-pus	Slight	3	5		13
14. M. C.	w	M	20	s	pap-pus	Slight	4	4		14
15. C. M.	w	F	22	s	pap	Slight	6	5		15
(16.) M. W.	w	F	18	s	Cys	Slight	4	4	Control	16
(17.) R. A.	w	F	21	s	pap	Slight	5	5	Control	17
18. J. B.	w	F	21	s	pap	Slight	5	4		18
19. B. H.	w	F	21	s	pap-pus	Moderate	5	5		19
(20.) H. G.	w	M	21	s	com-pap-pus	Slight	6	5	Control	20
21. R. H.	w	M	22	s	pap-pus	Slight	6	3		21
22. H. P.	w	M	20	s	com-pap-pus	Slight	2	2		22
23. D. S.	w	M	22	s	pap-pus	Slight	2	2		23
24. C. Z.	w	M	18	s	pap-pus	Moderate	6	5		24
25. H. J.	w	F	19	s	com-pap-pus	Slight	6	6	Identi-	x25
26. M. J.	w	F	19	s	com-pap-pus	Slight	6	6	cal Twins	26
27. H. H.	w	F	21	s	com-pap-pus	Slight	5	4		27
28. C. S.	w	F	21	s	pap	Slight	2	2		28
29. E. L.	w	F	18	s	com-pap-pus	Slight	6	5		x29
30. M. C.	w	F	22	s	com-pap	Slight	6	6		30
31. E. B.	w	F	19	s	pap	Slight	4	4		x31
32. P. L.	w	F	19	s	pap	Moderate	2	2		32
33. D. R.	w	M	19	s	pap-pus	Slight	5	5		33
34. C. H.	w	F	20	s	pap	Moderate	6	6		x34
35. C. F.	w	F	19	s	pap	Slight	6	5		35
36. A. T.	w	M	21	s	com	Moderate	6	4		36
37. S. P.	w	F	18	s	com-pap-pus	Slight	1	2		37
(38.) B. B.	w	F	24	s	pap-pus	Slight	5	5	Control	38
(39.) J. S.	w	F	18	s	com-pap-pus	Slight	6	4	Control	39
40. B. U.	w	F	21	s	com-pap-pus	Slight	2	2		40
41. B. K.	w	F	19	s	com-pap-pus	Moderate	6	6		41
42. R. M.	w	M	20	s	com-pap-pus	Moderate	4	4	1st mo.	
43. J. C.	w	M	24	m	com-pap-pus	Slight	2	2		x43

* Grading of lesions according to the degree of inflammatory reaction is based on an arbitrary scale as slight, moderate and severe.

† Parentheses indicate controls.

experiment were those already receiving treatment from other physicians and those whose disease was too mild to permit accurate evaluation of the response to therapy.

Of the 65 students who began the experiment, 43 stayed with it to completion. Information about the 22 subjects who dropped out of the experiment after one or two months, discouraged by their lack of improvement, is not included in our statistics. Pertinent data about the subjects who completed the experiment are listed in table 1.

Each patient was given a supply either of soluble gelatin capsules containing 100,000 international units of vitamin A or of placebo capsules[2] indistinguishable from those containing the vitamin, with instructions to take one daily. Because of the war shortage it was difficult to obtain placebo capsules; for this reason

TABLE 2

Results of the administration of vitamin A to eleven patients with senile keratosis

PATIENT	SEX	AGE	LENGTH OF TREATMENT	TIME ELAPSED BEFORE CHANGE IN SEVERITY OF LESIONS	DEGREE OF CHANGE IN SEVERITY OF LESIONS
			mos.	*mos.*	
1. R. D.	m	80	12		none
2. G. C.	m	77	8	8	slight
3. K. M.	f	75	6		none
4. K. V.	m	81	17	7	great
5. H. T.	m	77	7		none
6. M. B.	m	75	12	1	slight
7. C. C.	m	78	18	3	moderate
8. V. H.	m	80	6	5	slight
9. I. K.	m	75	16		none
10. C. O.	f	76	13	3	slight
11. T. O.	m	79	11	4	great

the number of controls is limited. The nurse who maintained confidential records was the only person who knew which patients were receiving placebos. The subjects were given no other treatment but were advised to continue any mode of self treatment in use at the beginning of the experiment.

The experiment ran from October 1947 to June 1948. The patients were examined from 2 to 6 times, at monthly intervals.

B. Experimental Therapy of Senile Keratoses.[3] The 20 subjects selected for the experiment were chosen from patients seen in the Dermatology Clinic of the Los Angeles County General Hospital. In every instance their lesions were of sufficient severity to make it possible to evaluate the results of therapy. Every patient was given a supply of capsules, each of which contained 50,000 internationa1

[2] Both the Vitamin A and the placebo capsules were supplied by Bioproducts Oreg. Ltd. of Warrenton, Oregon.

[3] From the University of Southern California, Department of Dermatology and the Los Angeles County General Hospital.

units of vitamin A, with instructions to take 3 daily. Nine of the 20 patients failed to carry the experiment through to completion. Data only on the 11 who

TABLE 3

Results of the administration of vitamin A to thirty-five patients with acne vulgaris

PATIENT	TYPE OF ACNE	SEVERITY OF LESIONS	TIME ELAPSED BEFORE CHANGE IN SEVERITY	DEGREE OF CHANGE IN SEVERITY	X—BECAME WORSE WHEN TRT. STOPPED—BETTER WHEN RESUMED
			mos.		
1. K. L.	com	moderate		worse	
2. J. F.	pap-pus	slight	1	great improvement	
3. E. W.	cys	slight	2	slight improvement	
4. J. H.	pap-pus	slight	1	moderate improvement	
5. J. Z.	com-pap-pus	moderate		no improvement	
6. R. G.	pap-pus	moderate		no improvement	
7. T. D.	pap-pus	moderate	3	great improvement	x
8. A. M.	com-pap-pus	moderate		no improvement	
9. L. M.	com-pap-pus	slight		no improvement	
10. V. N.	com-pap-pus	slight		no improvement	
11. M. C.	pap-pus	slight	2	slight improvement	
12. C. M.	pap-	slight	3	great improvement	
13. J. B.	pap	slight	1	great improvement	
14. B. H.	pap-pus	moderate	3	great improvement	
15. R. H.	pap-pus	slight	1	slight improvement	
16. H. P.	com-pap-pus	slight		no improvement	
17. D. S.	pap-pus	slight		no improvement	
18. C. Z.	pap-pus	moderate		no improvement	
19. H. J.	com-pap-pus	slight	1	moderate improvement	x Identical Twins
20. M. J.	com-pap-pus	slight		no improvement	
21. H. H.	com-pap-pus	slight	5	slight improvement	
22. C. S.	pap	slight		no improvement	
23. E. L.	com-pap-pus	slight	1	great improvement	x
24. M. C.	com-pap	slight	4	moderate improvement	
25. E. B.	pap	slight	3	slight improvement	x
26. P. L.	pap	moderate		no improvement	
27. D. R.	pap-pus	slight		no improvement	
28. C. H.	pap	moderate	1	great improvement	x
29. C. F.	pap	slight	1	great improvement	
30. A. T.	com	moderate	2	moderate improvement	
31. S. P.	com-pap-pus	slight		worse	
32. B. M.	com-pap-pus	slight		worse	
33. B. K.	com-pap-pus	moderate	1	moderate improvement	
34. R. M.	com-pap-pus	moderate	2	great improvement	Worse last mos.
35. J. C.	com-pap-pus	slight	2	moderate improvement	x

completed the experiment are included here (table 2). The duration of the experiment was 18 months. All patients were observed monthly or bi-monthly.

RESULTS

A. Experimental Therapy of Acne Vulgaris. Examination of table 3, which lists the results of administering vitamin A to 35 subjects with acne, discloses

that 20 patients displayed improvement in the eruption, ranging from slight to great, 12 showed no change and 3 exhibited an increase in the severity of the lesions. Improvement rarely occurred in less than two months while the four who improved while taking placebos all responded within one month. The response to ingestion of the vitamin bore no consistent relation to the severity of the eruption. Nine of the 20 subjects who showed improvement and 6 of the 12 who did not had lesions of the comedo type. Six of the 20 patients who showed improvement stated that the lesions had increased in severity when they failed to take the vitamin for a week or more and that the eruption grew better after they resumed treatment.

Table 4 shows that of the 8 patients with acne given placebos, 4 showed some degree of improvement and 4 showed no change in the severity of the eruption.

TABLE 4

Results of the administration of placebos to eight patients with acne vulgaris

PATIENT	TYPE OF ACNE	SEVERITY OF LESIONS	TIME ELAPSED BEFORE CHANGE	DEGREE OF CHANGE IN SEVERITY	COMMENT
			mos.		
1. M. B.	pap	slight	1	slight	
2. R. C.	pap	slight		none	
3. J. B.	pap	moderate	1	moderate	Improvement paralleled patient's avoiding chocolate
4. M. W.	cys	slight	1	great	
5. R. A.	pap	slight	1	great	
6. H. G.	com-pap-pus	moderate		none	
7. B. B.	pap-pus	slight		none	
8. J. S.	com-pap-pus	slight		none	

In all four subjects who exhibited improvement the change took place within one month.

B. Experimental Therapy of Senile Keratoses. The results of the experimental administration of vitamin A to 11 patients with senile keratoses are detailed in table 2. Seven showed some degree of improvement and 4 displayed no change in the character of the lesions.

COMMENT

It is of interest that a set of identical twins was included in the group of subjects with acne. The twin who received vitamin A showed moderate improvement with therapy and an increase in the severity of the eruption when the vitamin was replaced by placebos. Her sister showed no change in the severity of the lesions either with placebos or with vitamin A, but it should be pointed out that the vitamin was taken for only two months.

In evaluating the results of the vitamin A therapy of acne we took cognizance of two important factors, namely (1) that acne vulgaris affecting subjects 16 to 22 years of age tends to subside spontaneously, without therapy, and (2) our

series of patients was too small to yield results of statistical significance. The similarity in the proportions of patients who showed improvement after receiving vitamin A (57 per cent) and after receiving placebos (50 per cent) probably emphasizes the importance of psychologic factors in the treatment of acne rather than the true efficacy of vitamin A therapy. The fact that improvement in the subjects who received placebos occurred during the first month emphasizes the psychologic implication. It should be noted that 6 (30%) of those subjects who were distinctly benefited by ingestion of the vitamin experienced an increase in the severity of the eruption when treatment lapsed and a decrease when therapy was resumed. Obviously, study of a much larger number of subjects and controls will be necessary to establish the value of vitamin A as an adjunct to the therapy of acne vulgaris.

As to the experiment on senile keratoses, evaluation is made difficult by the small series of subjects. Yet the fact that the lesions of more than one half of the patients showed evidence of regression is sufficiently remarkable to stimulate further investigation of the effect of the vitamin on these precancerous lesions for which as yet no other systemic mode of therapy exists.

It may be of interest to note in passing that 1 of 3 additional patients with generalized keratoses presumably caused by the ingestion of arsenic showed great improvement after taking 150,000 international units of vitamin A daily for approximately six months, 1 showed slight improvement and 1 revealed no change in the severity of the eruption.

SUMMARY

Of 35 college students with acne who were given vitamin A, 20 showed improvement, 12 no change and 3 an increase in the severity of the eruption. Four of 8 controls given placebos exhibited improvement and 4 no change in the severity of the lesions.

Seven of 11 patients with senile keratoses showed improvement after treatment with vitamin A and 4 no change in the eruption. Two of 3 additional patients with arsenical keratoses responded favorably to the vitamin therapy.

Improvement of the eruption in all groups of subjects seemed not to be influenced by the type or severity of the lesions; improvement seldom occurred in less than two months.

Much larger series of controls and experimental subjects must be studied before statistically valid results can be obtained.

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